Elevated Plasma Beta-Endorphin Levels in Patients With Congestive Heart Failure

SEINOSUKE KAWASHIMA, MD, NAOSHIGE FUKUTAKE, MD, KATSUHIKO NISHIAN, MD, SUSUMU ASAKUMA, MD, TADAAKI IWASAKI, MD

Nishinomiya, Japan

Recent experimental studies show that the opioid system is important to the pathophysiology of cardiovascular impairment in congestive heart failure. Plasma beta-endorphin levels were measured in 37 patients with congestive heart failure and compared with those of 21 age- and gender-matched normal subjects. The relation of plasma beta-endorphin levels and cardiac function at rest and exercise capacity was assessed in 17 of the patients with dilated cardiomyopathy. Exercise capacity was determined by symptom-limited maximal treadmill exercise with expired gas analysis. Plasma beta-endorphin levels were elevated and correlated with the patients' New York Heart Association functional cardiac status (control: 14.0 ± 4.4 pg/ml; class II: 17.9 ± 3.6 pg/ml; class III: 28.3 ± 8.8 pg/ml; class IV: 46.7 ± 14.6 pg/ml, mean ± SD). No relation was found between plasma beta-endorphin levels and left ventricular systolic performance as assessed by M-mode and Doppler echocardiography. Plasma beta endorphin levels were negatively correlated with cardiac output determined by Doppler echocardiography and positively correlated with systemic vascular resistance ($r = -0.733$, $r = 0.747$, respectively, both $p < 0.001$), but not correlated with calf blood flow as measured by a plethysmography. A good correlation was found between plasma beta-endorphin levels at rest and exercise capacity. The correlations with peak oxygen consumption, anaerobic threshold, and peak rate-pressure product were $r = -0.721$, -0.672, and -0.674, respectively ($p < 0.01$).

The data show that plasma beta-endorphin levels are elevated in patients with congestive heart failure and reflect, to some degree, the severity of the disease.

(J Am Coll Cardiol 1991;17:53–8)

Endogenous opioids have analgesic, euphoric and addictive effects (1–3). It has become clear that endogenous opioids are essential to regulation of the cardiovascular system (4,5). Opioid peptides are found at sites related to autonomic actions and opioid receptors are densely concentrated in areas near the cardiovascular centers of the brain and hypothalamus (4). Endogenous opioids are involved in the pathogenesis of various types of shock, such as hemorrhagic shock, as well as hypertension (4–7). They also affect respiration and the secretion of vasopressin and other hormones (4,5,8).

Beta-endorphin is one of the major endogenous opioids and is derived from pro-opiomelanocortin, found in the pituitary (1–5,9). Liang et al. (10,11) reported that plasma levels of beta-endorphin are elevated in dogs with chronic congestive heart failure produced by pulmonary artery constriction and tricuspid valve avulsion. They also showed that the administration of the opioid receptor antagonist nalmefene resulted in improvement of the impaired hemodynamics in those dogs and suggested that endogenous opioids contribute to circulatory dysfunction in congestive heart failure. Clinically, however, the role of endogenous opioids in congestive heart failure remains unclear. No report, to our knowledge, has focused attention on beta-endorphin in patients with congestive heart failure.

The purposes of the present study were to determine 1) whether plasma beta-endorphin levels are elevated in patients with congestive heart failure, and 2) the relation of plasma beta-endorphin levels to the severity of cardiovascular abnormality and exercise capacity in these patients.

Methods

Study patients. The study was performed in 37 patients with congestive heart failure (29 men and 8 women) aged 22 to 77 years (mean ± SD, 56 ± 13). The underlying causes of heart failure were idiopathic dilated cardiomyopathy in 19, old myocardial infarction in 7 and valvular disease in 11. All patients had been symptomatic for at least 2 months and were treated with digitalis and diuretics. No patients had received adrenergic agonists or antagonists. Captopril had been given to four patients and was withdrawn in two of them before this study. Patients with a recent myocardial infarction (<3 months) and symptomatic angina pectoris were excluded. Twenty-one healthy subjects without cardiovascular disease (16 men and 5 women) aged 26 to 72 years

From the First Department of Medicine, Hyogo College of Medicine, Nishinomiya, Japan. This study was supported in part by a grand-in-aid for the encouragement of young researchers (01770620) from the Ministry of Education and Science and Culture, Tokyo, Japan.

Manuscript received March 5, 1990; revised manuscript received July 3, 1990, accepted July 18, 1990.

Address for reprints: Seinosuke Kawashima, MD, Hyogo College of Medicine, Nishinomiya, 663, Japan.

0735-1097/91/$3.50

JACC Vol. 17, No. 1
January 1991:53–8

(mean 50 ± 12) served as the control group. The study was approved by the Institutional Human Research Review Committee and each patient gave informed consent.

Plasma beta-endorphin levels. These were taken between 7:00 and 8:00 AM and were regarded as basal levels. The day-to-day variability of basal plasma beta-endorphin levels was determined in six control subjects and four patients with heart failure under relatively stable clinical conditions. Sequential blood sampling was performed on 2 days separated by 1 week.

In all patients, the basal plasma beta-endorphin levels were assessed in relation to functional cardiac status, determined according to the criteria of the New York Heart Association based on symptoms (12). To evaluate changes in endorphin levels with respect to changes in cardiac status with time in individual patients, we measured plasma beta-endorphin at baseline on admission and sequentially during follow-up periods of 2 months in eight patients.

Echocardiography. For detailed assessment of the role of beta-endorphins in the cardiovascular system, noninvasive studies of cardiac function were performed in the patients with dilated cardiomyopathy. After blood sampling, two-dimensional and pulsed Doppler echocardiography was performed. The studies were performed with the subjects in a semilateral position. The examination was carried out by using a B-mode image with the Toshiba SSH 65A system and 2.5 or 3.5 MHz transducer. Among the 19 patients with dilated cardiomyopathy, two were excluded from the study because of concomitant high-grade mitral regurgitation. Left ventricular end-diastolic and end-systolic dimensions were measured below the tips of the mitral leaflets. By Doppler echocardiography, duration of aortic flow was used as the left ventricular ejection time and the period from the beginning of the electrocardiographic QRS complex to the onset of aortic flow as the pre-ejection period. Fractional shortening (FS) of the left ventricle was calculated as (LVDd − LVDs)/LVDd × 100. Mean rate of circumferential shortening (Vcf) (circ/s) was calculated as (LVDd − LVDs)/(LVDd × LVET), where LVDd and LVDs = left ventricular end-diastolic and end-systolic dimension, respectively, and LVET = left ventricular ejection time. Cardiac output was determined by the Doppler left ventricular outflow method from the apical five-chamber view.

Plethysmography. Calf blood flow was obtained by strain-gauge plethysmography with the venous occlusion technique (13). Blood pressure was measured with a sphygmomanometer. Systemic vascular resistance was calculated by dividing the mean blood pressure (diastolic pressure plus one-third of the pulse pressure) by cardiac output.

Exercise capacity. Maximal exercise capacity was estimated in 16 of 17 patients with dilated cardiomyopathy in the postabsorptive state on the day of the noninvasive study. One patient was symptomatic at rest (class IV) and could not exercise. The patients underwent upright treadmill exercise to a symptom-limited maximum of dyspnea or fatigue. All patients studied were familiarized with the exercise program before the study. The exercise was carried out in the following 2-min stages: 1 = 1.5 km/h, 0% grade; 2 = 2 km/h, 0% grade; 3 = 2 km/h, 5% grade; 4 = 2.5 km/h, 5% grade; 5 = 3 km/h, 8% grade; 6 = 3.5 km/h, 10% grade; 7 = 4 km/h, 10% grade; 8 = 4.5 km/h, 10% grade; 9 = 5 km/h, 13% grade; and 10 = 5.5 km/h, 15% grade. Expired gas was collected and analyzed continuously with on-line breath-by-breath computer data acquisition (Westron Co.). Using the on-line computer, oxygen consumption ($\dot{V}O_2$), minute ventilation ($\dot{V}E$), carbon dioxide production ($\dot{V}CO_2$), end-tidal oxygen partial pressure, end-tidal carbon dioxide partial pressure and respiratory quotient (RQ) were measured. Heart rate, blood pressure and ECGs were monitored throughout the exercise test. As an expression of exercise capacity, the rate-pressure product at the time of peak $\dot{V}O_2$ was calculated. The anaerobic threshold was defined based on the criteria of Simonton et al. (14).

Measurements of plasma beta-endorphin. Blood sampling for measurements of basal plasma beta-endorphin was done with the patient in the supine position using an indwelling 18 gauge catheter inserted in an antecubital vein. Blood was taken 30 min after the catheter was placed and immediately introduced into chilled tubes containing EDTA anticoagulant. Blood was centrifuged for 15 min at 4°C at 760 *g* and plasma was stored at −40°C until use. One milliliter of plasma was concentrated and beta-endorphin was extracted using a column and antibody-coated Sepharose particles. Beta-endorphin was eluted with 0.025 N HCl from the column and measured by radioimmunoassay (INCSTAR Co.). In this assay system, cross reactivity with beta-lipntropin was less than 5%. Replicate measurements at our laboratory of plasma beta-endorphin had coefficients of variations of 10%.

Statistics. All values were expressed as mean values ± SD. A comparison of beta-endorphin levels among groups was made by one-way analysis of variance with Scheffé's multiple comparison test. Linear regression analysis using the least-squares method was conducted to compare plasma beta-endorphin levels with hemodynamic measurements and exercise capacity. A p value of ≤0.05 was considered statistically significant.

Results

Plasma beta-endorphin levels. The mean basal plasma beta-endorphin levels in control subjects was 14.0 ± 4.4 pg/ml. No control subject had a basal level exceeding 20 pg/ml. The mean level in patients with congestive heart failure, was 30.8 ± 15.9 pg/ml, significantly higher than that in control subjects ($p < 0.01$). Plasma beta-endorphin levels were found to be relatively stable throughout 1 week, the variation being within 20% in each subject.

The patients were divided into subgroups on the basis of their functional cardiac status (12). No patient was in class I. The plasma beta-endorphin levels were found to correlate with the functional cardiac status. Basal plasma beta-

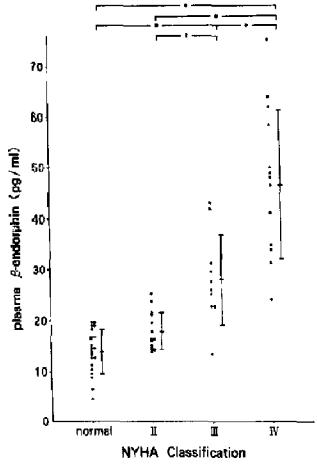


Figure 1. Functional cardiac status (New York Heart Association [NYHA] classification) versus plasma beta-endorphin levels in 21 control subjects and 37 patients with congestive heart failure. The mean ± SD is indicated by the solid bar for each functional class. *$p < 0.01$; †$p < 0.05$.

endorphin levels in patients with classes III and IV heart failure were significantly higher than those in control subjects (Fig. 1). In individual patients in whom sequential follow-up blood sampling was performed, plasma beta-endorphin levels changed with alteration in the patient's clinical status (Fig. 2).

Noninvasive hemodynamic variables and plasma beta-endorphin levels. The clinical characteristics and plasma beta-endorphin levels of the 17 patients with dilated cardiomyopathy are shown in Table 1; there were 15 men and 2 women, aged 24 to 76 years. Eight patients were in functional class II, five were in class III and four were in class IV. Plasma levels of beta-endorphin were correlated with functional cardiac status (class II: 16.0 ± 1.8 pg/ml; class III: 26.5 ± 10.3 pg/ml; class IV: 48.3 ± 13.1 pg/ml; $p < 0.01$ for class II versus IV and class II versus IV).

Hemodynamic values at rest were examined for correlation with plasma beta-endorphin levels. The patients exhibited decreased left ventricular performance with a large left ventricle. Neither blood pressure nor heart rate correlated with plasma beta-endorphin levels. Index of left ventricular systolic function did not correlate with plasma beta-endorphin ($r = -0.429$ for FS, -0.328 for mean Vcf and 0.116 for pre-ejection period/left ventricular ejection time)

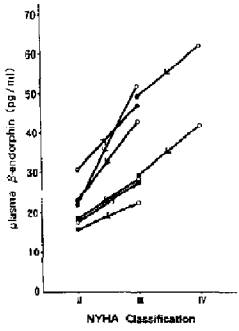


Figure 2. Changes in plasma beta-endorphin levels during a follow-up period of 2 months in eight patients with congestive heart failure. Open circles represent plasma beta-endorphin levels on admission and closed circles those obtained 2 months later.

(Fig. 3). Neither left ventricular end-diastolic nor end-systolic dimension correlated with plasma beta-endorphin level ($r = 0.226$, and 0.330, respectively) (Fig. 4). The ratio of early to late peak flow velocity during diastole in the Doppler transmitral flow pattern was measured in 11 patients with sinus rhythm and showed no correlation with plasma beta-endorphin ($r = -0.027$). A negative correlation was noted between beta-endorphin levels and Doppler-derived cardiac output ($r = -0.743$) (Fig. 5). There was a positive correlation between beta-endorphin levels and systemic vascular resistance ($r = 0.747$). There was no correlation between beta-endorphin levels and calf blood flow ($r = -0.422$).

Exercise capacity and plasma beta-endorphin. Basal plasma beta-endorphin levels were closely correlated with exercise capacity (Fig. 6). The higher the plasma levels, the lower the exercise capacity. This good correlation could still be observed after excluding patients older than 70 years to minimize age-related variability in exercise performance (15). After the exclusion, the correlation with peak oxygen consumption, anaerobic threshold and peak rate-pressure product were $r = -0.770$ ($p < 0.01$), -0.689 ($p < 0.01$), and -0.677 ($p < 0.05$), respectively.

Discussion

The present study shows that plasma levels of beta-endorphin are elevated in patients with congestive heart failure. This is in agreement with previous experimental data (10,11) obtained from conscious dogs with congestive heart failure. Plasma beta-endorphin levels also correlated with functional cardiac status and exercise capacity.

JACC Vol. 17, No. 1
January 1991:53–8

Table 1. Characteristics of 17 Patients with Cardiomyopathy Grouped According to Cardiac Functional Class

Pt. No.	Age (yr)	Sex	HR (beats/min)	BP (mm Hg)	Plasma Beta-Endorphin (pg/ml)
			Class II		
1	65	M	56	116/74	14.8
2	58	M	82	114/70	16.8
3	42	F	71	126/84	14.6
4	42	M	74	122/86	13.8
5	53	M	65	130/84	16.4
6	37	M	72	118/72	17.0
7	72	M	68	130/80	19.4
8	41	F	76	152/88	15.1
Mean	51.3		71.8		16.0
SD	12.8		5.6		1.8
			Class III		
9	56	M	68	98/60	22.8
10	56	M	80	120/78	13.6
11	44	M	70	126/70	41.6
12	76	M	68	110/66	29.0
13	42	M	70	110/76	25.5
Mean	54.8		71.2		26.5
SD	13.5		5.0		10.3
			Class IV		
14	65	M	86	110/68	56.4
15	58	M	68	106/70	62.0
16	24	M	104	96/76	34.0
17	74	M	96	156/92	40.9
Mean	54.3		88.5		48.3
SD	21.8		15.5		13.1

BP = blood pressure; F = female; HR = heart rate; M = male.

Secretion of beta-endorphin. The precursor of beta-endorphin is pro-opiomelanocortin, a common precursor with adrenocorticotropin (ACTH), and mainly located in the pituitary gland (1–3). Beta-endorphin and adrenocorticotropin are released together into the peripheral circulation from the pituitary gland in response to various stresses (1–3,9). In addition to stress, plasma beta-endorphin levels are regulated by circadian rhythm and a negative feedback system (1,2,5,9). Neurohumoral factors such as corticotropin-releasing factor and catecholamines are believed to be involved in the secretion of beta-endorphin from the pituitary gland during stress. It has been reported that plasma levels of beta-endorphin increase during a hypovolemic state (4,16). Therefore, although the precise mechanism is unclear, underperfusion in various tissues probably acts to stimulate secretion of beta-endorphin in patients with heart failure.

Beta-endorphin and cardiovascular function. Sympathetic nervous activity is augmented in heart failure (17–20). Although the heightened adrenergic drive may play a detrimental role in the late phase of heart failure, it operates to compensate for hemodynamic abnormalities in heart failure. Endogenous opioids such as beta-endorphin are closely

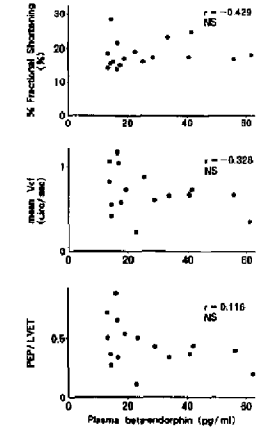
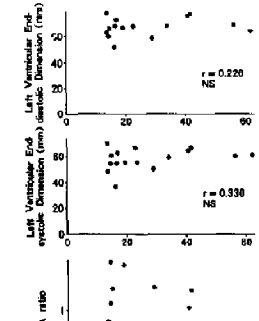


Figure 3. Lack of correlation of plasma beta-endorphin levels with indexes of left ventricular performance at rest. LVET = left ventricular ejection time; mean Vcf = mean rate of circumferential shortening; PEP = pre-ejection period.

Figure 4. Lack of correlation of plasma beta-endorphin level with left ventricular end-diastolic and end-systolic dimensions and ratio of early to late peak velocity (E/A ratio) during diastole in the transmitral Doppler flow pattern.



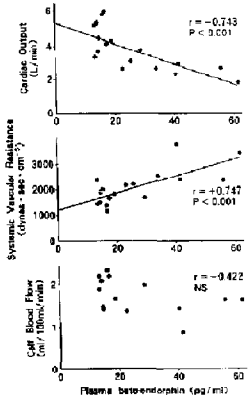


Figure 5. Correlation of plasma beta-endorphin with cardiac output at rest, systemic vascular resistance and calf blood flow.

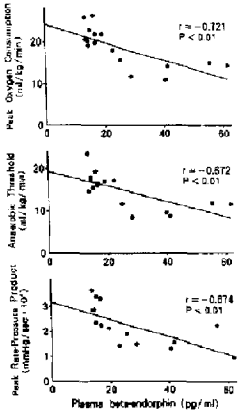


Figure 6. Correlation of plasma beta-endorphin with indexes of exercise performance during treadmill exercise testing.

related to the sympathetic nervous system both in brain and peripheral tissues (4,21). Liang et al (10) demonstrated that nalmefene, an opioid receptor antagonist, increased cardiac output and improved tissue perfusion mainly by neutralizing the inhibitory action of opioids on the sympathetic nervous system in dogs with heart failure. Recent studies (22) also show that endogenous opioids exert local depressant effects on the heart. Thus, increased beta-endorphin may be a deleterious factor in congestive heart failure accompanied by an activated sympathetic nervous system.

Relation to cardiovascular function. To examine whether plasma beta-endorphin contributes to hemodynamic abnormality in congestive heart failure, a correlation between plasma beta-endorphin levels and cardiovascular function was sought. For the assessment, dilated cardiomyopathy was chosen because it has characteristics relatively typical of impaired ventricular function and was believed suitable for echocardiographic assessment of ventricular shape. Plasma endorphin levels did not correlate with any variable of left ventricular function, including ventricular contractility. Thus, elevated plasma beta-endorphin levels do not play a major role in the control of ventricular function in patients with heart failure. Plasma beta-endorphin levels were positively correlated with systemic vascular resistance and negatively with cardiac output. Therefore, either hypoperfusion may function as a stimulus of beta-endorphin release or beta-endorphin may contribute to hypoperfusion as reflected by decreased cardiac output and increased systemic vascular resistance in congestive heart failure. Opioid receptor antagonists have been shown (4–6) to increase cardiac output and decrease systemic vascular resistance in various types of shock. A study using an opioid receptor antagonist should be conducted to clarify the causal role of beta-endorphin for the hypoperfusion in heart failure.

Beta-endorphin and exercise capacity. Plasma beta-endorphin levels were correlated with exercise capacity as expressed by peak oxygen consumption, anaerobic threshold, and peak rate-pressure product. Exercise capacity is a realistic index of clinical disability and prognosis in patients with heart failure (23,24). Therefore, the good correlation of plasma beta-endorphin levels with exercise capacity and functional cardiac status suggests that beta-endorphin levels are a marker of the severity of heart failure (25).

Although a good correlation was noted between exercise capacity and plasma levels of beta-endorphin, cause and effect cannot be inferred. Beta-endorphin levels increase during exercise, and this may be related to perception of pain and regulation of ventilation during exercise (26,27). But whether increased plasma beta-endorphin levels influence exercise capacity in heart failure remains unclear. Naloxone, an opiate receptor antagonist, fails to modify exercise performance in healthy men (28,29), but no information is available as to whether naloxone can alter exercise tolerance in patients with congestive heart failure. Conversely, increased plasma levels of beta-endorphin may simply reflect the severity of heart failure. Further studies are needed to clarify the role of beta-endorphin as a factor determining exercise capacity in patients with congestive heart failure.

JACC Vol. 17, No. 1
January 1991:53–8

Conclusions. In recent years, increasing attention has been directed to the neurohumoral factors in congestive heart failure; these factors contribute importantly to the symptoms of heart failure. Plasma beta-endorphin levels are elevated in patients with congestive heart failure. Along with other neurohumoral factors, plasma beta-endorphin levels reflect the severity of congestive heart failure. Plasma beta-endorphin levels were shown to be correlated with cardiac functional status and exercise capacity. Whether beta-endorphin can serve as a marker of patient prognosis, as in the case of norepinephrine, remains to be determined.

References

1. Akil H, Watson SJ, Young E, Lewis ME, Khachaturian H, Walker JM. Endogenous opioids: biology and function. Annu Rev Neurosci 1984;7: 223–55.
2. Tilders FJH, Berendsen F, Smelik PG. Control of secretion of peptides related to adrenocortin, melanocyte-stimulating hormone and endorphin. Front Horm Res 1985;14:161–96.
3. Olson GA, Olson RD, Kastin AJ, Coy DH. Endogenous opiates: 1981. Peptides 1982;3:1039–72.
4. Holaday JW. Cardiovascular effects of endogenous opiate systems. Annu Rev Pharmacol Toxicol 1983;23:541–94.
5. Johnson MW, Mitch WE, Wilcox CS. The cardiovascular actions of morphine and the endogenous opioid peptides. Prog Cardiovasc Dis 1985;27:435–50.
6. Holaday JW, Faden AI. Naloxone reversal of endotoxin hypotension suggests role of endorphins in shock. Nature 1978;275:450–1.
7. Kunos G, Farsang C, Ramirez-Gonzales M. Beta-endorphin: possible involvement in the antihypertensive effect of central receptor activation. Science 1981;211:82–4.
8. Weil JV, McCullogh RE, Kline JS, Sodal IE. Diminished ventilatory response to hypoxia and hypercapnea after morphine in normal man. N Engl J Med 1975;292:1103–6.
9. Guillemin R, Vargo T, Rossier J, et al. Beta-endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. Science 1977;197:1367–9.
10. Liang C-s, Imai N, Stone CK, Woolf PD, Kawashima S, Tuttle RR. The role of endogenous opioids in congestive heart failure: effects of nalmefene on systemic and regional hemodynamics in dogs. Circulation 1987;75:443–51.
11. Sakamoto S, Stone CK, Woolf PD, Liang C-s. Opiate receptor antagonist in right-sided congestive heart failure: naloxone exerts salutary hemodynamic effects through its action on the central nervous system. Circ Res 1989;65:103–14.
12. The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels, 6th ed. New York: Little Brown & Co., 1964:110–4.
13. Cowley AJ, Stainer K, Rowley JM, Hampton JR. Abnormalities of the peripheral circulation and respiratory function in patients with severe heart failure. Br Heart J 1986;55:75–80.
14. Simonton CA, Higginbotham MB, Cobb FR. The ventilatory threshold: quantitative analysis of reproducibility and relation to arterial lactate concentration in normal subjects and in patients with chronic congestive heart failure. Am J Cardiol 1988;62:100–7.
15. Meifer SE, Ashton JJ, Moeschberger ML, Unverferth DV, Leier CV. An analysis of the determinants of exercise performance in congestive heart failure. Am Heart J 1987;113:1207–17.
16. Vargish T, Beamer K. Hemodynamic effects of naloxone in early canine hypovolemic shock (abstr). Circ Shock 1984;13:48.
17. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. Am J Cardiol 1978;41:233–43.
18. Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JA. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormonal levels and their relation to hemodynamic abnormalities in congestive heart failure. Am J Cardiol 1982;49:1659–66.
19. Parmley WW. Pathophysiology and current therapy of congestive heart failure. J Am Coll Cardiol 1989;13:771–85.
20. Packer MP. Neurohormonal interactions and adaptations in congestive heart failure. Circulation 1988;77:721–30.
21. Scadt JC, Gaddis RR. Endogenous opiate peptides may limit norepinephrine release during hemorrhage. J Pharmacol Exp Ther 1982;221:282–8.
22. Lechner RB, Gurll NJ, Reynolds D. Intracoronary naloxone in hemorrhagic shock: dose-dependent stereospecific effects. Am J Physiol 1985; 249:H272–7.
23. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting ventricular performance in heart failure. Am J Cardiol 1981;47:33–9.
24. Benge W, Litchfield RL, Marcus ML. Exercise capacity in patients with severe left ventricular dysfunction. Circulation 1980;61:955–9.
25. Francis GS, Goldsmith SR, Cohn JN. Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. Am Heart J 1982;104:725–31.
26. DeMeirler K, Naaktgeboren N, Van Steirteghem A, Gorus F, Olbrecht J, Block P. Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. Eur J Appl Physiol 1986;55:5–8.
27. Farrell PA, Gates WK, Maksud MG, Morgan WP. Increases in plasma beta-endorphin/beta-lipotropin immunoreactivity after treadmill running in humans. J Appl Physiol 1982;52:1245–9.
28. Paulev PE, Thorboll JE, Nielsen U, et al. Opioid involvement in the perception of pain due to cadurance exercise in trained man. Jpn J Physiol 1989;39:67–74.
29. Surbey GD, Andrew GM, Cervenko FW, Hamilton PP. Effects of naloxone on exercise performance. J Appl Physiol 1984;57:674–9.